The relief effect of botulinum toxin-a for spastic iliopsoas of cerebral palsy on children


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Abstract. – OBJECTIVE: This work intended to observe the effect of injecting botulinum toxin type A (BTX-A) for relieving spastic iliopsoas of cerebral palsy on children, and to investigate the improvement of this method for the motor function in these children.

PATIENTS AND METHODS: From July 2006 to August 2012, 37 children with spastic iliopsoas cerebral palsy were received rehabilitation therapy. The age ranged from 3 to 15 years. The control group were treated by conventional physical therapy (PY). The experimental group were treated not only by the conventional physical therapy, but also BTX-A injection. The dose of BTX-A injection was according to the weight of the child and the Modified Ashworth Scale (MAS). The dose of the injection ranged from 15 IU to 45 IU with the average dose 31.2±13.9 IU.

RESULTS: There was no significant difference between two the groups on ages, weight and MAS, GMFM (Gross Motor Function Measure) and extension angle of hip joints before treatment. In both groups, the Modified Ashworth Scale decreased, GMFM and extension angle of hip joints increased after eight weeks. In the control group, the GMFM improved significantly. In the experimental group, MAS, GMFM and extension angle of hip joints changed significantly after therapy. There was significant difference between two groups in MAS, GMFM and extension angle of hip joints after two months.

CONCLUSIONS: The BTX-A injection can relieve iliopsoas spasticity of cerebral palsy on children efficiently. This therapy can help children to correct abnormal gait and to improve their motor function.

Key Words:
Cerebral palsy, Spasticity, BTX-A, Iliopsoas, Gait analysis.

Introduction

Cerebral palsy (CP) is a common disabling adolescent disease, spastic cerebral palsy is the most common cerebral palsy type and accounts for 60-70%. Spasms impede normal motor development in patients, and also result in contractures, deformity, pain, and other complications. Spasticity relief has become the focus of rehabilitation treatments for cerebral palsy.

Spasticity treatment includes rehabilitation, oral administration of muscle relaxants, nerve blocks, intrathecal injection of Baclofen, surgery, and serial casting. Among them, nerve blocks are widely accepted, with botulinum toxin type A (BTX-A) as the most commonly used drug. BTX-A block is considered one of the optimal approaches for spastic cerebral palsy, due to its rapid effect, great selectivity, and few side effects.

Spasticity iliopsoas will cause the abnormality of extension angle of hip joints in child with CP. This abnormality will interfere the standing and walking of children patients and hamper the normal motor function development of children.

The methods of relieving spasticity iliopsoas are rather limited because of the difficulty on locating the muscle and very few people received the BTX-A injection method. This work intended to observe the effect of injecting BTX-A for relieving spastic iliopsoas of cerebral palsy on children, and to investigate the promotion of this method for the motor function in these patients.

Patients and Methods

37 children CP patients were collected from July 2006 to August 2012 in our hospital, including 23 boys and 14 girls. The age ranged from 3-15 years old with the average age is 5.92. The diagnostic criteria and clinical classification were according to the standard established by 2004 national symposium on cerebral palsy in children.

Inclusion criteria: Children were all spastic CP patients with iliopsoas muscle high tension. They can walk over 10 steps independently and ac-
companied with the flexion posture of hip. Their flexion posture of hip were mainly caused by spasticity of iliopsoas muscle. Exclusive criteria: Iliopsoas muscle of children become contracture (hip joint cannot unbend), or hamstring having spasticity (Ashworth scoring ≥ 2 grade), or gluteus maximus amyasthenia (muscle strengthen ≤ 3 grade), or have epilepsy, or have allergic constitution.

**Grouping**

The children patients were randomly grouped into control group and experimental group according to visiting time. In the control group (n=20), there was 12 male patients and 8 female patients. The age ranged from 3-15 years old with the average age 6.02 ± 3.11. The weight ranged from 14.5-42 kg with the average weight 21.4±17 kg. In the experimental group (n=17), there was 11 male patients and 6 female patients. The age ranged from 4-13 years old with the average age 5.86 ± 2.23. And the weight ranged from 15-40 kg with the average weight 23.1±4.67 kg. The two groups have no significant difference in gender, age and weight.

The 20 children patients of control group were received conventional physical therapy (PT) rehabilitation training. In the experimental group, besides conventional PT rehabilitation training, they were injected BTX-A in iliopsoas muscle.

**Drug and Materials**

BTX-A powder was purchased from Lanzhou Institute of Biological Products Co., Ltd. Each dose has 100IU BTX-A. The BTX-A powder were stored at −5°C to −20°C with avoiding light. The BTX-A powder was dissolved with saline to 50 IU/ml before using.

Nerve block insulative needles (made in Japan), injection syringe, electric paste, surface electrode and wire. The stimulator was produced from Shanghai Huayi Medical Instrument Corporation with the type of G6805-2A therapeutic instrument. In the treatment, the stimulator was adopted continuous wave, with the pulse frequency 2.667-83.333 Hz, current intensity 0-15 mA, 6V.

**Operation Method**

**Positioning**

The projection area of the selected muscle on body surface was located based on the anatomy position. The anode of the stimulator was fixed by band on surface of the buttoc. The pulse frequency was set at 3 Hz and the current intensity was temporarily set at 10-15 mA. Then the cathode was used to search the projection area of the inguinal iliopsoas muscle, and at the same time, adjusting the current intensity, until find the position that can cause the iliopsoas muscle contract with minimal current intensity. Then, the position was marked as injecting site by gentian violet.

**Injection**

The current intensity was adjust to 3 mA, and keep the pulse frequency unchanged. After conventional disinfection, the nerve block insulative needles was connected with stimulator and was injected into the subcutaneous tissue. Then, adjusting the depth of the needle and the current intensity until using the minimal current intensity can cause the muscle maximal contraction, the BTX-A will be injected in.

**Injecting Point and Dose**

The dose of the BTX-A was according to the grade of the muscle spasticity (muscular tension) and the weight of the children patient. According to the Modified Ashworth Scale, the muscle with grade 1 and 1+ will be injected 1-1.5 U BTX-A per kg. The muscle with grade 2 and 3 will be injected 1.5-2 U BTX-A per kg. The injecting point will be 1-2. The total injecting dose will be 15-45 IU every time with the average dose 31.2±13.9 IU. If the muscle was scored grade 4 according to the modified Ashworth system, the muscle has become contracture and will not be injected BTX-A.

**Evaluation**

Before therapy, the muscular tension of iliopsoas muscle, motor function and the range of hip joint were assessed. After 8 weeks of therapy, the assess was made again.

The method of evaluating spasticity adopt the Modified Ashworth Scale (MAS). The grade of this scale was transformed to score system: 1 grade 1 score, 1+ grade 2 score, 2 grade 3 score, 3 grade 4 score, 4 grade 5 score. The method of evaluating motor function adopt GMFM method (Gross Motor Function Measure). Before therapy, they were assessed once, and one year later, they were assess again.

The range of hip joint was evaluated by gait analysis method. The gait analysis was evaluated by the rehabilitation department of China Reha-
Rehabilitation Research Center. The gait analysis system was based on the digital video and digital imaging processing technology. The ranges of hip joint were gathered from one side of the body when the foot initial contact in gait cycle, when the foot kept flat, when they stood, when the heel left the ground, when the toe left the ground. The average maximal range of stride phase was also gathered. Then, the average range of both side of hip joint was calculated.

Statistical Method
The data was shown in the type of (\(\bar{x} \pm s\)). The data was analysis by SPSS 13.0 (SPSS Inc., Chicago, IL, USA) and the One-Sample Kolmogorov-Smirnov test was adopted to normal distribution test. After test, all the data fitted normal distribution \((p > 0.05)\). Paired-samples \(t\) test was adopted in intra-group comparison and independent-samples \(t\) test was adopted in group comparison. Significant difference was set at \(\alpha = 0.05\).

Results

Base Line
The weight, age, MAS before therapy, GMFM scoring, and the range of the hip joint of the two patient groups have no significant difference \((p > 0.05)\) (Table I).

The MAS Comparison Between Two Patient Groups After 8 Weeks Therapy
In the control group, although the MAS of the children patients were slightly decreased after rehabilitation therapy, the MAS had no significant difference between before and after rehabilitation therapy \((p > 0.05)\). However, in the experimental group, the MAS of the children patients have significant difference between before and after rehabilitation therapy \((p < 0.05)\). After 8 weeks of rehabilitation therapy, there are significant difference between control group and experimental group \((p < 0.05)\) (Table II).

Table I. The base line comparison between two patient group.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Age (year)</th>
<th>Weight (kg)</th>
<th>MAS before therapy</th>
<th>GMFM before therapy</th>
<th>The range of hip joint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>20</td>
<td>6.02 ± 3.11</td>
<td>21.4 ± 5.17</td>
<td>2.31 ± 1.07</td>
<td>63.2 ± 11.45</td>
<td>31.3 ± 4.65</td>
</tr>
<tr>
<td>Experimental group</td>
<td>17</td>
<td>5.86 ± 2.23</td>
<td>23.1 ± 4.67</td>
<td>2.14 ± 0.93</td>
<td>64.5 ± 9.76</td>
<td>28.6 ± 3.97</td>
</tr>
<tr>
<td>(p)</td>
<td>0.38</td>
<td>0.73</td>
<td></td>
<td>0.08</td>
<td>0.19</td>
<td>0.51</td>
</tr>
</tbody>
</table>

The GMFM Comparison Between the Two Group
After 8 weeks rehabilitation therapy, the GMFM of the two groups have shown significant difference compared with before therapy \((p < 0.05)\). The increase of GMFM in the experimental group was higher than that in the control group. The increase of GMFM score in the two group has significant difference \((p < 0.01)\) (Table III).

The Range of Hip Joint Comparison Between Two Groups
After 8 weeks rehabilitation therapy, the range of hip joint of the two groups have decreased compared before therapy. But in the control group, there was not significant difference \((p > 0.05)\), while in the experimental, there was significant difference \((p < 0.05)\). The decrease of range in experimental group was smaller than that of control group. The decrease of range between the two groups has significant difference \((p < 0.01)\) (Table IV).

Discussion
The choice of interventions for the management of the movement disorders associated with CP in patients is extensive and varied. The interventions include oral medications, selective dorsal rhizotomy (SDR)\(^{11}\), intrathecal baclofen (ITB)\(^{12}\) chemodenervation, and so on. It can be difficult at first sight to determine on what criteria the choice should be made between many competing options.

Clinical experience of BTX-A in treatment of spasticity in patients spans more than a decade with the pioneering trials from Koman et al in the United States\(^{13}\) and Graham et al in the United Kingdom\(^{14}\). There are seven Botulinum toxin serotypes (A-F) of which only types A and B have been reported in children with CP. The differences in serotypes have been described in detail elsewhere in this volume.
The mechanisms underlying spasms are relatively complex, and it is generally considered that central nervous system injury leads to disorder or abnormally high central regulation of the spinal stretch reflex, ultimately resulting in overly strong or sensitive traction reflex. Spasms are responsible for delayed motor development and abnormal posture in patients with cerebral palsy. However, cerebral palsy-induced spasms do not exist in all muscles, but often occur as a result of increased muscle tension in some muscles. For example, the majority of adolescent patients with spasms exhibited significantly high tension in the calf triceps muscle, but spasms were not present in the anterior tibial muscle, which resulted in abnormal posture, such as an equinovarus foot. Spasm relief in the calf muscle has been shown to correct equinovarus foot.  

BTX-A bring about chemical denervation by blocking acetylcholine release. It first binds to a membrane protein on presynaptic cell surface called synaptic vesicle protein (SV2). This is mediated by the C-terminal domain of the heavy chain. The toxin is subsequently internalized by an energy-dependent receptor-mediated endocytic process. The disulfide bond is cleaved, and the light chain is released across the endosomal membrane into the cytoplasm of the nerve terminal with the help of the translocation domain. Finally the light chain cleaves SNAP-25 (synaptosomal-associated protein of 25 kDa), one of the three SNARE (soluble NSF-attachment protein receptor) proteins. SNAP-25 is required for the docking of acetylcholine vesicles on the inner side of the nerve terminal plasma membrane. As a result, muscle spasms may stop or be reduced. Previous studies have shown that BTX-A injections into the calf triceps muscle significantly reduces muscle tension and expands joint activity. In addition, gait and movement are also improved.  

The flexion posture of hip joints is a common symptom in CP children patients and iliopsoas

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**Table II.** The MAS comparison between the two groups after one month of therapy.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>MAS before therapy</th>
<th>MAS after 8 weeks of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>20</td>
<td>2.31 ± 1.07</td>
<td>1.97 ± 0.62*</td>
</tr>
<tr>
<td>Experimental group</td>
<td>17</td>
<td>2.14 ± 0.93</td>
<td>1.02 ± 0.18b</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>0.08</td>
<td>0.023</td>
</tr>
</tbody>
</table>

*Note: Compared with before therapy in the same group, *p* = 0.094, *p* = 0.004.

**Table III.** The GMFM comparison between the two groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Before therapy</th>
<th>After 8 weeks therapy</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>20</td>
<td>63.2 ± 11.45</td>
<td>66.1 ± 13.35*</td>
<td>2.9 ± 0.85</td>
</tr>
<tr>
<td>Experimental group</td>
<td>17</td>
<td>64.5 ± 9.76</td>
<td>72.7 ± 10.17*</td>
<td>8.2 ± 3.46*</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>0.19</td>
<td>0.04</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Note: Compared with before therapy in the same group, *p* = 0.038, *p* = 0.013. C: Compared with control group, *p* = 0.002.

**Table IV.** The range of hip joint comparison between the two groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Before therapy (degree)</th>
<th>After 8 weeks therapy (degree)</th>
<th>Difference (degree)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>20</td>
<td>31.3 ± 4.65</td>
<td>26.2 ± 3.18*</td>
<td>5.1 ± 0.56</td>
</tr>
<tr>
<td>Experimental group</td>
<td>17</td>
<td>28.6 ± 3.97</td>
<td>15.7 ± 2.15*</td>
<td>12.9 ± 1.28*</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>0.51</td>
<td>0.02</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Note: Compared with before therapy in the same group, *p* = 0.239, *p* = 0.021. C: Compared with control group, *p* = 0.001.
spasticity is a major factor to cause this abnormal posture. The conventional method to correct the abnormal posture is rehabilitation training. This method is to excise the joint passively to decrease the extension of iliopsoas, but the curative effect is very limited and could not correct the abnormal gait.

The injection of BTX-A is an effective method to relieve the muscle spasticity of CP children patients. Many researches report that BTX-A injection can decrease the extension of muscle and can expand the range of joint\textsuperscript{16,18,21}. Also, it can improve the walking gait and motor function. Because of the deep location of iliopsoas in body and the topography complexity, fewer patients received the BTX-A injection therapy in China.

In this study, we adopted a relative accurate locating method to make sure the BTX-A be injected in the iliopsoas. This method ensures the curative effect of BTX-A.

In our patients selection, we have chosen these children whose abnormal gait was mainly caused by the spasticity of iliopsoas. The abnormality of the range of hip joint may be caused by spasticity of hamstring and gluteus maximus amyasthenia. In this situation, the relief on spasticity of iliopsoas will not improve the abnormality of gait. Thus, we should analyze distinguish the cause of this disease.

In the process of analyzing the disease, we need to check the relative muscle strength and muscular tension. If the iliopsoas has become contracture, the contractural tendon could not be prolonged by the injection of BTX-A and always do not have curative effect. This symptom is not suitable for BTX-A injection therapy. If the abnormality range of hip joint is mainly cause by spasticity of hamstring, the relief of the spasticity should be considered. If the strength of gluteus maximus below or equal to 3 grade, this can also cause the abnormality range of hip joint. In this situation, also the BTX-A injection could not improve the extension of hip joint. Only if the gluteus maximus have somewhat antigravity strength and the disease is mainly caused by spasticity of iliopsoas, the BTX-A therapy could have good curative effect.

In this study, the two patients groups have no significant differences in age and weight. This suggested that the two groups have the same conditions. The no significant difference in MAS, GMFM and the range of hip suggested that the two groups have comparability in the grade of spasticity and motor function. Thus, based on the reasonable control group, confounding factors were excluded as much as possible and made the conclusions are more convincing.

In the control group, although the MAS of the children patients were slightly decreased after rehabilitation therapy, the MAS had no significant difference between before and after rehabilitation therapy. However, in the experimental group, the MAS of the children patients have significant difference between before and after rehabilitation therapy. After 8 weeks of rehabilitation therapy, there is a significant difference between control group and experimental group. These results suggested that BTX-A injection can relieve the spasticity of iliopsoas.

After 8 weeks of rehabilitation therapy, the GMFM of the two groups have shown significant difference compared with before therapy. The increase of GMFM in the experimental group was higher than that in the control group. The increase of GMFM score in the two group has significant difference. This suggested that the motor function in experimental group have been improved more that control group. The rehabilitation training combined with BTX-A could improve the curative effect.

Gait analysis showed that, after 8 weeks of rehabilitation, the range of hip joint of the two groups have decreased compared before therapy. But in the control group, there was not significant difference, while in the experimental, there was significant difference. The decrease of range in experimental group was smaller than that of control group. The decrease of range between the two groups has significant difference. This suggested that the abnormality gait in experimental group has been preferable corrected.

There are few reports about this method in worldwide. Westhoff et al\textsuperscript{22} have reported that they have injected the BTX-A into iliopsoas from inguinal region based on the ultrasonic location. They have injected BTX-A for 10 CP children patients, 4 hereditary spastic paraplegia patients, and 5 Legg-Calve-Perthes disease patients. The method has somewhat curative effect on these patients and does not have side effect.

Depedibi et al\textsuperscript{19} used the same ultrasonic location method on 18 CP patients for injecting BTX-A. After 5 weeks, the MAS and the range of hip joint increased. After 12 weeks, the MAS and WeeFIM (walking subscale – Functional independence Measure for children) somewhat increased. The results of their studies agree with our studies.
Conclusions

Rehabilitation training combined with BTX-A injection, can relieve the spasticity of iliopsoas of children patients, increase the motor function and improve the gait. It is a worth popularizing rehabilitation method.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References